



# EPIDEMIOLOGY BULLETIN

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# The Importance of Careful Antibiotic Use

#### Introduction

In the United States, the rate of drug resistant bacteria is increasing dramatically. Over the past five years, the rate of penicillin resistance increased by more than 300% and the rate of cefotaxime resistance increased by more than 1000%. Pneumococci have developed resistance to cephalosporins, erythromycin, trimethoprim-sulfamethoxazole, quinolones, and other agents. The only remaining antibiotic that is effective against all pneumococci is vancomycin.

The increased use of antibiotics has likely contributed to these trends. Recent antibiotic use has been shown in multiple studies to be a risk factor for invasive disease with drug resistant pneumococci. Otitis media with penicillin non-susceptible strains has an increased risk of bacteriologic and clinical treatment failure, even with commonly used cephalosporins. The fear is that several bacterial infections may soon be untreatable.

The 2000 Session of the Virginia General Assembly passed House Joint Resolution No. 384 (see box, page 2, for complete text). That resolution directs the Commissioner of Health to urge health professionals to adopt the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommendations in their practices. In response to that Resolution, this issue of the *Virginia Epidemiology Bulletin* will be devoted to the problem of antibiotic resistance. Recommendations by

the CDC/AAP for the careful use of antibiotics will be presented.

#### **Practice Tips**

The CDC has developed some tips to follow to make promoting judicious antibiotic use part of your routine clinical practice. They suggest the following responses when patients ask for antibiotics to treat viral infections:

- Explain that unnecessary antibiotics can be harmful.
- Share the facts. That is, explain that viral infections are never cured by antibiotics.
- Build cooperation and trust.
- Encourage active management of illness by planning the treatment of symptoms with the patient and describing the expected normal time course of the illness. Tell the patient to come back if the symptoms persist or worsen.

 Be confident with the recommendation to use alternative treatments, such as analgesics and decongestants, nutrition and

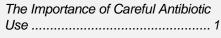
CDC further suggests that medical care providers create an office environment to promote the reduction in antibiotic use by following these steps:

hydration.

- Talk about antibiotic use at 4 and 12 month well child visits.
- Start the educational process in the waiting room through the use of videotapes, posters, or other materials.
- Involve office personnel in the educational process. Your office staff can help change patient attitudes by reinforcing your messages.
- Use the CDC/AAP pamphlets and principles to support your treatment decisions. Provide information to help patients understand when the risks of using antibiotics outweigh the benefits.

The CDC/AAP guidelines on judicious treatment of otitis media, rhinitis and sinusitis, pharyngitis, and cough illness and bronchitis. CDC/AAP patient materials may be ordered from the CDC website at w w w . c d c . g o v / n c i d o d / d b m d / antibioticresistance/materials.htm.

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#### **HOUSE JOINT RESOLUTION NO. 384**

Endorsing the recommendations of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) regarding the use of antibiotics.

Agreed to by the House of Delegates, March 6, 2000 Agreed to by the Senate, March 2, 2000

WHEREAS, antibiotic-resistant infections are more likely to produce adverse health outcomes and are more costly to treat than susceptible infections; and

WHEREAS, the widespread use of antibiotics has increased the type and incidence of bacteria that are resistant to treatment by antibiotics; and

WHEREAS, antibiotic resistance is caused by the overuse of antibiotics in general and the overuse of selected agents in particular; and

WHEREAS, over the past five years, the rate of penicillin resistance increased by more than 300 percent, and the rate of cefotaxime resistance increased by more than 1,000 percent; and

WHEREAS, patients infected with antibiotic-resistant strains of bacteria can require hospitalization when otherwise unnecessary and be subject to an increased rate of death; and

WHEREAS, antibiotic resistance increases pharmaceutical costs through inappropriate prescribing of antibiotic agents and increases total health care costs through the additional hospitalizations and other forms of additional medical care required in the treatment of antibiotic-resistant strains of bacteria; and

WHEREAS, the federal CDC and the AAP have developed recommendations for health care professionals regarding best practices for the judicious use of antibiotics; now, therefore, be it

RESOLVED by the House of Delegates, the Senate concurring, That the recommendations of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) regarding the use of antibiotics be endorsed; and, be it

RESOLVED FURTHER, That the Commissioner of Health be requested to urge each health care professional and each managed care plan operating in Virginia to adopt the CDC/AAP recommendations in their practices and their formularies; and, be it

RESOLVED FINALLY, That the Clerk of the House of Delegates transmit copies of this resolution to the Commissioner of Health and the Executive Director of the Joint Commission on Health Care, requesting that the Commissioner forward copies of this resolution to each local area health director and that the Executive Director forward copies of this resolution to appropriate health care organizations along with the request that the information be used to raise public awareness about antibiotic resistance in order that all may be apprised of the sense of the General Assembly in this matter.



# Stemming the tide of antibiotic resistance: Recommendations by the CDC /AAP to promote judicious antibiotic use.

### APPROPRIATE TREATMENT SUMMARY

DIAGNOSIS	CDC/AAP Principles of Appropriate Antibiotic Use
Otitis Media	<ol> <li>Classify episodes of otitis media as acute otitis media (AOM) or otitis media with effusion (OME). Only treat proven AOM.</li> <li>Antibiotics are indicated for treatment of AOM, however, diagnosis requires         <ul> <li>documented middle ear infection.</li> <li>and, signs or symptoms of acute local or systemic illness.</li> </ul> </li> <li>Don't prescribe antibiotics for initial treatment of OME         <ul> <li>treatment may be indicated if bilateral effusions persist for 3 months or more.</li> </ul> </li> </ol>
Rhinitis and Sinusitis	<ul> <li>Rhinitis: <ol> <li>Antibiotics should not be given for viral rhinosinusitis.</li> <li>Mucopurulent rhinitis (thick, opaque, or discolored nasal discharge) frequently accompanies viral rhinosinusitis. It is not an indication for antibiotic treatment unless it persists without improvement for more than 10-14 days.</li> </ol> </li> <li>Sinusitis: <ol> <li>Diagnose as sinusitis only in the presence of:  — prolonged nonspecific upper respiratory signs and symptoms (e.g. rhinorrhea and cough without improvement for &gt;10-14 days), or  — more severe upper respiratory tract signs and symptoms (e.g. fever &gt;39° C, facial swelling, facial pain).</li> <li>Initial antibiotic treatment of acute sinusitis should be with the most narrow-spectrum agent which is active against the likely pathogens.</li> </ol> </li></ul>
Pharyngitis	<ol> <li>Diagnose as group A streptococcal pharyngitis using a laboratory test in conjunction with clinical and epidemiological findings.</li> <li>Antibiotics should not be given to a child with pharyngitis in the absence of diagnosed group A streptococcal infection.</li> <li>A penicillin remains the drug of choice for treating group A streptococcal pharyngitis.</li> </ol>
Cough Illness and Bronchitis	<ol> <li>Cough illness/bronchitis in children rarely warrants antibiotic treatment.</li> <li>Antibiotic treatment for prolonged cough (&gt;10 days) may occasionally be warranted:         <ul> <li>Pertussis should be treated according to established recommendations.</li> <li>Mycoplasma pneumoniae infection may cause pneumonia and prolonged cough (usually in children older than 5 years); a macrolide agent (or tetracycline in children 8 years or older) may be used for treatment.</li> <li>Children with underlying chronic pulmonary disease (not including asthma) may occasionally benefit from antibiotic therapy for acute exacerbations.</li> </ul> </li> </ol>

#### When parents demand antibiotics...

- Provide educational materials and share your treatment rules to explain when the risks of antibiotics outweigh the benefits.
- Build cooperation and trust:
  - $\sqrt{\text{don't dismiss the illness as "only a viral infection."}}$
  - $\sqrt{}$  explicitly plan treatment of symptoms with parents.
  - $\sqrt{\text{give parents a realistic time course for resolution.}}$
  - $\sqrt{\text{prescribe analgesics and decongestants, if appropriate.}}$



# Otitis media with effusion does not require antibiotic treatment

### **OTITIS MEDIA**

Differentiating Acute Otitis Media (AOM) from Otitis Media with Effusion (OME): A tool for promoting judicious antibiotic use.

Always use pneumatic otoscopy or tympanometry to confirm middle ear effusion

No effusion
Not OME or AOM



Yes, effusion present

Signs or symptoms of AOM —including ear pain, fever, and bulging yellow or red TM

Yes





No

#### **AOM**

Presence of effusion (always use pneumatic otoscopy or tympanometry)

with

signs or symptoms of acute infection (ear pain, fever, or bulging yellow or red TM).



Treatment Choose narrow spectrum drugs first.

Amoxicillin remains highly effective and is recommended as the first-line antibiotic by most experts.<sup>12</sup>

Only consider antibiotic prophylaxis for recurrent AOM as defined by  $\ge 3$  distinct, well documented episodes in 6 months (or  $\ge 4$  in 12 months).

Residual effusion after AOM normally persists for up to 6 weeks - no evidence of benefit from treatment in these cases.

#### **OME**

Presence of effusion (including immobility of the tympanic membrane)

without

signs or symptoms of acute infection. Nonspecific signs and symptoms (rhinitis, cough, diarrhea) are often present.



**Treatment** 

Antibiotics are not required for initial treatment.<sup>3</sup>

Meta-analysis of all known studies showed only marginal short term benefit, and no long term benefit (>1 month) of antibiotic treatment.<sup>4</sup>

Share this algorithm with parents. Explain when the risks of using antibiotics outweigh the benefits.

Avoiding unnecessary treatment for OME would save up to 6-8 million courses of antibiotics each year.<sup>3</sup>

#### References

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- 2. Barnett ED, Klein JO. The problem of resistant bacteria for the management of acute otitis media. Ped Clin N America 1995;42:509-17.
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- 4. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. JAMA 1993;270:1344-51.



When parents request antibiotics for rhinitis or the "common cold" ... Give them an explanation, not a prescription.

### RHINITIS VERSUS SINUSITIS

#### Remember:

Children have 2-9 viral respiratory illnesses per year.<sup>1</sup>

In uncomplicated colds, cough and nasal discharge may persist for 14 days or more — long after other symptoms, such as sneezing and sore throat, have resolved.

Controlled studies do not support antibiotic treatment of mucopurulent rhinitis.<sup>2</sup>

Antibiotics do not effectively treat URI, or prevent subsequent bacterial infections.<sup>3</sup>

## Don't overdiagnose sinusitis

Though most viral URIs involve the paranasal sinuses, only a small minority are complicated by bacterial sinusitis.

# Avoid unnecessary treatment by using strict criteria for diagnosis:<sup>3</sup>

Symptoms of rhinorrhea or persistent daytime cough lasting <u>more</u> than 10-14 days <u>without</u> <u>improvement</u>.

<u>or</u>

Severe symptoms of acute sinus infection:

- fever (>39°C) with purulent nasal discharge
- facial pain or tenderness
- periorbital swelling

### **Treating sinusitis:**

■ Target likely organisms with first line drugs:

Amoxicillin, Amoxicillin/Clavulanate4

■ Use shortest effective course:

Should see improvement in 2-3 days. Continue treatment for 7 days after symptoms improve or resolve (usually a 10-14 day course).<sup>5</sup>

■ Consider imaging studies in recurrent or unclear cases:

But remember that some sinus involvement is frequent early in the course of uncomplicated viral URI — so interpret studies with caution.

Share the CDC/AAP principles and pamphlets with parents to help them understand when antibiotic treatment risks outweigh the benefits.

- rhinorrhea, fever, and cough are symptoms of viral URI
- changes in mucous to yellow, thick, or green are the natural course of viral URI, NOT an indication for antibiotics.<sup>6</sup>
- treating viral URI will not shorten the course of illness or prevent bacterial infection.<sup>3</sup>

#### References

- 1. Monto AS, Ullman BM. Acute respiratory illness in an American community. JAMA 1974;227:164-9.
- 2. Todd JK, Todd N, Damato J, Todd WA. Bacteriology and treatment of purulent nasopharyngitis: a double blind placebo-controlled evaluation. Pediatr Infect Dis J 1984;3:226-32.
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- 4. Avorn J, Solomon D. Cultural and economic factors that (mis)shape antibiotic use: the non-pharmacologic basis of therapeutics. Ann Intern Med 2000;133:128-35.
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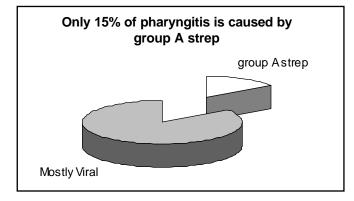
# To avoid antibiotic resistance: treat only proven group A strep

### **PHARYNGITIS**

"If you are entirely comfortable selecting which pharyngitis patients to treat 10 days with penicillin, perhaps you don't understand the situation."

- Stillerman and Bernstein, 1961

Most sore throats are caused by viral agents.<sup>1</sup>



■ Clinical findings alone do not adequately distinguish Strep vs. Non-Strep pharyngitis.²

BUT, prominent rhinorrhea, cough, hoarseness, conjunctivitis, or diarrhea suggest a VIRAL etiology.<sup>3</sup>

 Antigen tests (rapid Strep kits) or culture should be positive before beginning antibiotic treatment.

Experts suggest confirming negative results on antigen tests with culture.<sup>4</sup>

Experts discourage treatment pending culture results,<sup>4,5</sup> but if you do...

- Make sure to stop antibiotics when culture is negative.
- Discourage parents from saving antibiotics.

# If an antibiotic is prescribed:

■ Use a penicillin as treatment for group A strep.<sup>6</sup>

NO group A strep are resistant to penicillin. Treatment is 90% effective at elimination of strep, and may be higher in the prevention of acute rheumatic fever (ARF). Carriers are at very low risk for both ARF and spreading infection.<sup>6</sup>

■ Use erythromycin if penicillin allergic.

Remember that most cases with clinical signs of strep, like exudate and adenopathy, are viral.

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- 1. Tanz RR, Shulman ST. Diagnosis and treatment of group A streptococcal pharyngitis. Semin Pediatr Infect Dis 1995;6:69-78.
- 2. Poses RM, Cebul RD, Collins M et al. The accuracy of experienced physicians' probability estimates for patients with sore throat: implications for decision making. JAMA 1985;254:925-29.
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- 5. Middleton DB, D'Amico FD, Merenstein JH. Standardized symptomatic treatment versus pencillin as initial therapy for streptococcal pharyngitis. J Pediatr 1988;113:1089-94.
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# Cough illness in the well-appearing child: Antibiotics are NOT the answer.

### COUGH ILLNESS/BRONCHITIS<sup>1</sup>

Cough illness/bronchitis is principally caused by viral pathogens.<sup>2</sup> Airway inflammation and sputum production are non-specific responses and do not imply a bacterial etiology.

Authors of a meta-analysis of six randomized trials (in adults) concluded that antibiotics were ineffective in treating cough illness/bronchitis.<sup>3</sup>

Antibiotic treatment of upper respiratory infections do not prevent bacterial complications such as pneumonia.<sup>4</sup>

#### ■ Do not use antibiotics for:

Cough <10-14 days in well-appearing child without physical signs of pneumonia.

## **■** Consider antibiotics only for:

Suspected pneumonia, based on fever with focal exam, infiltrate on chest x-ray, tachypnea, or toxic appearance.

Prolonged cough (>10-14 days without improvement) may suggest specific illnesses (e.g. sinusitis) that warrant antibiotic treatment.<sup>5</sup>

Treatment with a macrolide (erythromycin) may be warranted in the child older than 5 years when mycoplasma or pertussis is suspected.<sup>6</sup>

## **■** When parents demand antibiotics...

Acknowledge the child's symptoms and discomfort.

Promote active management with non-pharmacologic treatments.

Give realistic time course for resolution.

Share the CDC/AAP principles and pamphlets with parents to help them understand when the risks of antibiotic treatment outweigh the benefits.

#### References

- 1. OBrien KL, Dowell SF, Schwartz B, Marcy SM, Phillips WR, Gerber MA. Cough illness/bronchitis principles of judicious use of antimicrobial agents. Pediatrics 1998;101:178-81.
- 2. Chapman RS, Henderson FW, Clyde WA, Collier AM, Denny FW. The epidemiology of tracheobronchitis in pediatric practice. Am J Epidemiol 1981;114:789-97.
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# Virginia Cancer Registry to Notify Patients

In response to a law passed by the 2000 General Assembly, the Virginia Cancer Registry (VCR) will begin sending information about the registry to cancer patients diagnosed on or after January 1, 2001. The law requires VCR to notify a patient within 30 days of receiving a report of his cancer. Some questions about this process are answered below.

#### Who will be notified?

The VCR will notify any patient diagnosed on or after January 1, 2001, and reported by a Virginia hospital, clinic, laboratory, or physician. The mailing will occur within 30 days of receipt of a completed case record. The VCR plans to notify each person only once, regardless of the number of reports received or additional cancers later diagnosed. Parents of minor patients will receive notification of their child's report. No notification will be sent if at the time of report, the VCR can verify a patient is deceased. Not all cases reported to the VCR are considered to be cancer, such as certain in situ tumors. In the informational materials, special care has been taken to note that not every condition reported to the VCR is cancerous and that this notification does not contradict any information provided by their physician.

#### How will notification occur?

Patients will be mailed an introductory letter, an informational flyer, and a copy of §2.1-378 of the Patient Privacy Act. The contents of the letter and flyer are mandated under the Patient Notification Law, and include "the purpose, objectives, reporting requirements, confidentiality policies and procedures of the statewide cancer registry, including, but not limited to, continued surveillance and investigation procedures and ... a copy of §2.1-378 of the Privacy Protection Act" (*Code of Virginia* §32.1-71.02).

## How will notification affect my facility or office?

Patient materials clearly state that providers report under state mandate (§32.1-70), and thus your reporting does not reflect a breach of patient confidentiality. Ultimately you are protected from liability for reporting under §32.1-38 of the *Code of Virginia*. The Virginia Cancer Registry is prohibited under §32.1-41 from releasing the names of reporting medical care providers. Patients will not be able to call the VCR and be told which specific provider reported his or her record.

However, you may want to be prepared to describe the benefits received from the practice of cancer registration, in terms of statistical data about the occurrence, detection, treatment, and survival of cancer among Virginians in different areas and populations. Patients should be assured that the VCR protects their confidentiality the same way you do and will not release any information that identifies them unless for a study on ways to prevent or decrease future cancer morbidity and mortality, and then only if the Health Commissioner approves the study and if the researcher will protect the data to the same extent.

# Can my patient view his or her information maintained by the VCR?

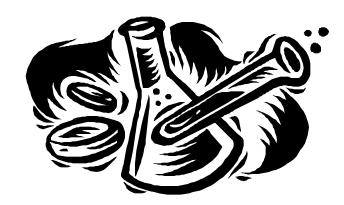
Yes. The VCR will have a procedure in place by which an individual can come to the Registry with proper identification and view or obtain a copy of his or her case record.

**Total Cases Reported, August 2000** 

				Region	ıs	Total Cases Reported Statewide, January through August			
Disease	State	NW	N	SW	C	E	This Year	Last Year	5 Yr Avg
AIDS	52	4	11	7	16	14	505	555	716
Campylobacteriosis	69	15	15	10	8	21	385	437	441
E. coli 0157:H7	18	4	10	3	0	1	43	44	42
Giardiasis	36	3	16	4	3	10	256	261	233
Gonorrhea	962	46	73	103	209	531	6656	6340	6099
Hepatitis A	14	1	6	1	1	5	102	103	129
B, acute	9	0	0	2	3	4	101	63	78
C/NANB, acute	0	0	0	0	0	0	3	10	12
HIV Infection	58	3	18	1	6	30	468	537	646
Lead in Children <sup>†</sup>	117	10	7	18	55	27	488	276	397
Legionellosis	5	1	0	2	1	1	17	17	16
Lyme Disease	24	2	14	4	1	3	95	76	44
Measles	0	0	0	0	0	0	2	3	2
Meningococcal Infection	1	0	0	0	0	1	35	35	38
Mumps	3	0	1	1	1	0	8	8	10
Pertussis	11	2	0	1	0	8	44	17	22
Rabies in Animals	50	15	7	5	11	12	388	344	362
Rocky Mountain Spotted Fever	1	1	0	0	0	0	4	12	15
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	138	12	53	10	27	36	631	850	702
Shigellosis	68	2	26	28	11	1	308	74	230
Syphilis, Early <sup>§</sup>	25	0	0	16	1	8	194	271	484
Tuberculosis	8	1	7	0	0	0	183	189	213

Localities Reporting Animal Rabies This Month: Accomack 3 raccoons; Amherst 1 skunk; Augusta 1 bat, 3 skunks; Bath 1 raccoon; Bland 1 raccoon; Chesapeake 1 cat; Fairfax 1 bat, 1 raccoon, 1 skunk; Gloucester 1 raccoon; Goochland 1 fox; Greensville 1 bat; Halifax 1 raccoon, 1 skunk; Hanover 1 bat, 1 mink; Henrico 2 raccoons; Highland 1 raccoon, 1 skunk; James City 2 foxes, 1 skunk; Loudoun 2 foxes; Louisa 1 skunk; Lynchburg 1 groundhog, 1 skunk; Mecklenburg 1 cat; Montgomery 1 raccoon; Northampton 3 raccoons; Prince Edward 1 raccoon; Prince George 1 raccoon; Prince William 1 bat, 1 raccoon; Rockingham 1 cat, 1 groundhog, 2 skunks; Shenandoah 1 skunk; Stafford 1 raccoon, 1 skunk; Westmoreland 1 cat.

\*\*Occupational Illnesses:\* Asbestosis 45; Lead Exposure 9; Pneumoconiosis 11.



<sup>\*</sup>Data for 2000 are provisional. †Elevated blood lead levels ≥10µg/dL.

<sup>§</sup>Includes primary, secondary, and early latent.

#### **Total Cases Reported, September 2000**

	State	Regions					Total Cases Reported Statewide, January through September		
Disease		NW	N	SW	C	E	This Year	Last Year	5 Yr Avg
AIDS	69	3	20	7	24	15	574	633	810
Campylobacteriosis	73	28	14	10	5	16	457	487	511
E. coli 0157:H7	13	3	1	6	3	0	56	57	50
Giardiasis	65	11	32	8	5	9	321	316	280
Gonorrhea	1103	65	92	150	309	487	7658	6922	7077
Hepatitis A	16	0	5	4	3	4	118	119	149
B, acute	23	2	6	3	5	7	124	69	89
C/NANB, acute	0	0	0	0	0	0	3	10	14
HIV Infection	84	7	41	3	8	25	551	632	740
Lead in Children <sup>†</sup>	92	6	7	15	39	25	581	335	483
Legionellosis	10	3	1	3	0	3	27	24	18
Lyme Disease	29	2	20	2	2	3	124	94	56
Measles	0	0	0	0	0	0	2	3	2
Meningococcal Infection	1	0	1	0	0	0	36	40	42
Mumps	0	0	0	0	0	0	8	8	11
Pertussis	27	9	3	0	1	14	71	17	30
Rabies in Animals	55	9	9	11	15	11	443	406	423
Rocky Mountain Spotted Fever	1	0	0	0	1	0	5	12	21
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	148	250	41	22	23	37	770	985	852
Shigellosis	38	0	11	24	2	1	341	94	268
Syphilis, Early§	24	0	3	5	7	9	218	287	535
Tuberculosis	10	0	3	1	2	4	196	223	242

Localities Reporting Animal Rabies This Month: Accomack 1 raccoon; Amherst 1 skunk; Augusta 2 skunks; Bedford 2 raccoons, 1 skunk; Buckingham 3 skunks; Chesapeake 1 raccoon; Chesterfield 2 raccoons, 2 skunks; Essex 1 fox; Fairfax 2 bats, 1 fox, 1 raccoon, 1 skunk; Fauquier 1 bat, 1 skunk; Floyd 1 skunk; Fredericksburg 1 fox; Gloucester 1 raccoon, 1 skunk; Hanover 1 skunk; Henrico 1 bat, 1 raccoon; Henry 1 raccoon, 1 skunk; Hopewell 3 raccoons; King George 1 raccoon; Loudoun 2 raccoons; New Kent 1 raccoon; Northampton 1 raccoon; Nottoway 1 skunk; Pittsylvania 1 raccoon, 1 skunk; Prince William 2 raccoons; Pulaski 1 cat; Rapphannock 1 cow; Rockingham 1 raccoon; Stafford 1 bat; Virginia Beach 1 raccoon; Williamsburg 1 raccoon; Wythe 1 cat; York 2 raccoons.

Occupational Illnesses: Asbestosis 124; Lead Exposure 15; Pneumoconiosis 5; Silicosis 1.

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<sup>\*</sup>Data for 2000 are provisional. †Elevated blood lead levels ≥10µg/dL.

<sup>§</sup>Includes primary, secondary, and early latent.